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## A case of photodistributed multicentric reticulohistiocytosis: correlation with multiphoton microscopy imaging.

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To the Editor,

A 52-year-old female presented with a photodistributed, mildly pruritic rash developing over a course of days. Closer examination demonstrated faint erythematous papules coalescing into confluent erythema in a photodistribution (Figure 1a). She denied any other systemic symptoms including joint pain. The differential diagnosis included connective tissue disease, polymorphic light eruption, phototoxic or photoallergic reactions, pellagra, or porphyria. A biopsy was taken, demonstrating a collection of multiple histiocytes and multinucleated giant cells throughout the dermis abutting the dermoepidermal junction. Sections seen at a higher magnification revealed the presence of large cells with eccentric nuclei and ample ground-glass cytoplasm. Immunohistochemical analysis demonstrated the cytoplasmic expression of CD68 in these cells. Lesional cells were negative for S100 and CD1a. Histologically, this was consistent with a diagnosis of multicentric reticulohistiocytosis. At the time of biopsy follow-up, the patient had begun developing characteristic dorsal hand lesions and mild arthralgias (Figure 1b). A thorough workup to assess for underlying malignancy or connective tissue disease was negative. The patient was subsequently started on methotrexate and alendronate, resulting in a significant reduction in her erythema, arthralgia, distal interphalangeal joint prominence, and hand lesions after 2 months.

Multicentric reticulohistiocytosis is a rare cutaneous and systemic proliferating non-Langerhans histiocytosis for which the cause is unknown [1]. It typically presents with insidious symmetric joint pain progressing to a debilitating mutilating arthritis. In the majority of cases, joint findings precede the cutaneous manifestations of skin-colored to red-brown papulonodular lesions on the face and dorsal hands (e.g. the pathognomonic coral beading sign) [2–4]. In 25% of cases, there is an association with malignancy which may be concurrent with or follow the presentation of multicentric reticulohistiocytosis. In rare cases, multicentric reticulohistiocytosis may present like connective tissue disease, with patients having features mimicking dermatomyositis including Gottron's papules, shawl sign, heliotrope rash, malar erythema extending to the nasolabial fold, and nailfold erythema.

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When dermatomyositis-like cutaneous findings are biopsied, they demonstrate histopathologic findings of multicentric reticulohistiocytosis, rather than dermatomyositis [2].

A multiphoton microscopy (MPM) tomograph (MPTflex; JenLab GmbH, Germany) was utilized to image one of the patient's skin lesions. Examination of en-face images of the papillary dermis revealed an infiltrate of cells with intensely fluorescent cytoplasm. At a depth of 130  $\mu\text{m}$ , two large cells (20  $\mu\text{m}$ ) were visualized showing identifiable nuclei; one of which presented an eccentric nucleus. This is correlated with histologic findings (Figure 2).

Multiphoton microscopy (MPM) is a laser-scanning optical imaging technique that has been recently introduced in clinical research for applications related to *in vivo*, non-invasive skin imaging [5]. MPM contrast in skin is derived from second harmonic generation (SHG) of collagen and two-photon excited fluorescence (TPEF) of tissue components such as the co-factors NADH and FAD, elastin, keratin, and melanin. Due to its contrast mechanism, MPM provides dual-color images that distinguish cellular features from the extra-cellular matrix, generating 3D, sub-micron resolved label-free images of skin.

Ultrastructural studies with electron microscopy of multicentric reticulohistiocytosis have been done previously by Perrin and coworkers corroborating that the infiltrate is composed by large cells with an irregular contour [6]. Of note multiple Golgi complex and mitochondria were found.

MPM provided us with a relatively rapid *in vivo* assessment of one of the lesions in this patient. Examination of the acquired digital images revealed the presence of large cells with large and intensely fluorescent cytoplasm; High levels of NADH and FAD due to an intense intracytoplasmic metabolic activity might account for the strong cytoplasmic fluorescence seen in the histiocytes in this case. These features correlate with the histological findings seen in this case.

To our knowledge, this is the first reported use of multiphoton microscopy in a histiocytic disorder. MPM of other photosensitive dermatoses have yet to be characterized. As MPM could identify characteristic nuclei suggestive of histiocytosis, MPM may be a promising non-invasive technique for the diagnosis of MRH or other histiocytic dermatoses. Further studies correlating MPM to routine histology are needed.

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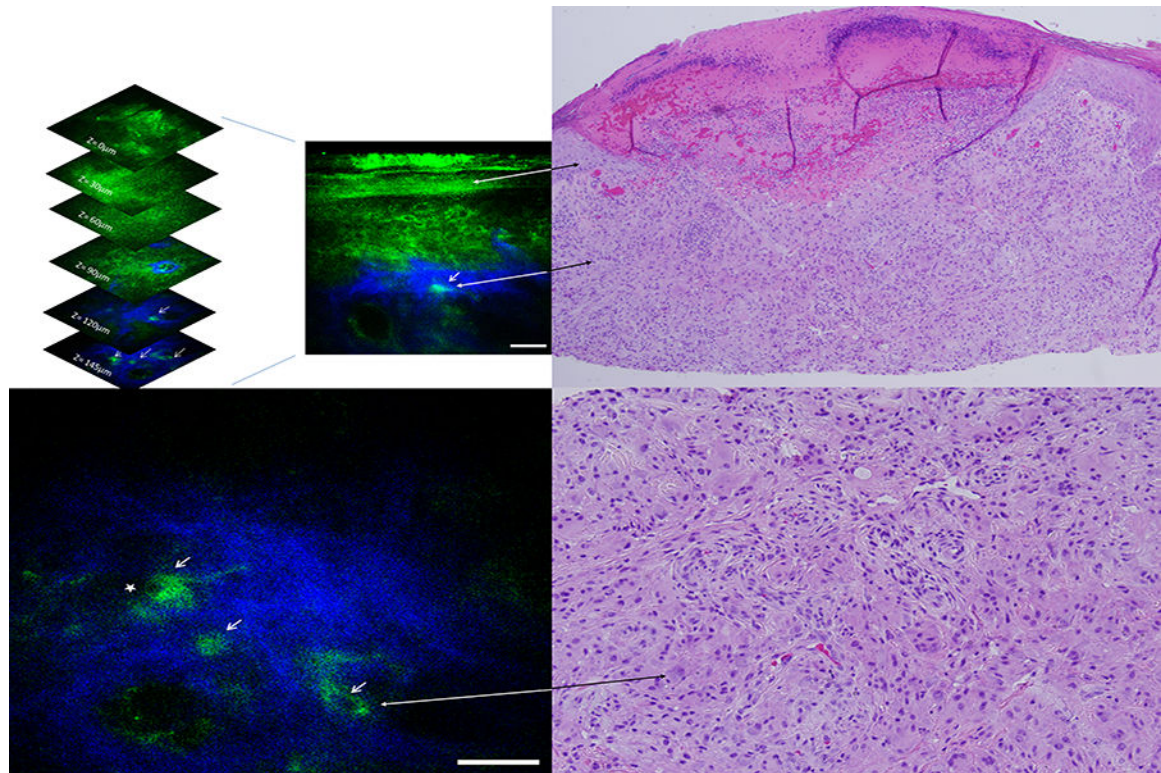




**Figure 1.**

a) Photodistributed erythema composed of confluent erythematous smooth papules. b) Characteristic waxy pink papules on the dorsal aspect of the hand





**Figure 2.**

A) Multiphoton microscopy (MPM) en-face images (x-y scans) of the stratum corneum at  $z = 0 \mu\text{m}$ , keratinocytes in the stratum spinosum at  $z = 60 \mu\text{m}$ , cells with intensely fluorescent and ample cytoplasm are seen at 120 and 140  $\mu\text{m}$  (arrows) Cross-sectional view(x-z scan) corresponding to a vertical plane through the same interrogating volume shown on the left and (Scale bar is 30  $\mu\text{m}$ ) B) en face MPM image at the level of the papillary dermis showing an infiltrate composed of cells with intensely fluorescent cytoplasm (arrows). Note that one of these cells presents an eccentric nucleus (star). (Scale bar is 30  $\mu\text{m}$ ). Histologic correlates on low and high power are shown with arrows demonstrating epidermis, inflammatory infiltrate and large histiocytes with eccentric nuclei.